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Article

Development of metformin HCl granules using brown flaxseed mucilage as a retardant polymer: effects of polymer and drug ratio

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Flaxseed (*Linum usitatissimum* L.) is the seed of a multipurpose plant of pharmaceutical interest, as its mucilage can be used as a natural matrix to develop extended-release dosage forms and potentially replace synthetic polymers. In this study, a 3^2 factorial design with two replicates of the central point was applied to optimize the development of extended-release granules of metformin HCl. The total fiber content of the mucilage as well as the friability and dissolution of the formulations were evaluated. The lyophilized mucilage presented a high total fiber content (42.63%), which suggests a high efficiency extraction process. Higher concentrations of the mucilage and metformin HCl yielded less friable granules. In addition, lower concentrations of metformin HCl and higher concentrations of the mucilage resulted in slower drug release during the dissolution assays. The release kinetics for most formulations were better represented by the Hixson-Crowell model, while formulations containing a higher concentration of the mucilage were represented by the Korsmeyer-Peppas model. Nonetheless, five formulations showed a longer release than the reference HPMC formulation. More desirable results were obtained with a higher concentration of the mucilage (13–18%) and a lower concentration of metformin (40%).

Keywords: Extended-release granules, Flaxseed mucilage, Metformin HCl.

INTRODUCTION

Flax (*Linum usitatissimum* L.) is one of the most important crops known to mankind, because almost all parts of the plant can be commercially used for the manufacture of durable consumer goods. For example, flaxseed is well known for its oil content, and is a commonly used medium to prepare high-quality oil paints (MacFadyen, 2018). It is also known as a modern functional food owing to its high content of α-linolenic acid (ALA, omega-3 fatty acid), lignans, and fiber (Goyal *et al.*, 2014). Flax seeds can be found in two main colors, yellow and brown; although the two variants are very similar, some differences have been observed. Traditionally, brown seeds have higher contents of linolenic acid (Mittapalli, Rowland, 2003), stearic acid, and tocopherols as well as an enhanced antioxidant capacity and stability compared to yellow seeds (Barroso *et al.*, 2014).

In addition, flaxseed in general contains some lesser-known substances: a mix of polysaccharides (mainly pectins or hemicelluloses) and proteoglycans, which are collectively referred to as the mucilage. These hydrophilic polymers are essential to the ecology of a number of different plant species, mainly assisting in the dispersal and germination process (Western, 2012). These substances are currently the topic of various research papers, reflecting the high value of flaxseed on the market. Mucilages of different origins

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are currently being used or being researched for use in the food industry, owing to their structuring, texturizing, emulsifying, and thickening properties (Soukoulis, Gaiani, Hoffmann, 2018). Additionally, mucilages have been studied by the pharmaceutical industry as a novel polymer matrix suitable for the manufacture of extended-release and/or mucoadhesive dosage forms (Yadav, Jain, 2015; Hasnain *et al.*, 2018; Ghumman, Noreen, tul Muntaha, 2020; Rocha *et al.*, 2021a). Furthermore, it has already been established that one way to increase flaxseed oil production yields is to extract the polysaccharides prior to the extraction of the oil (Ziolkovska, 2012). Therefore, it may be commercially viable to produce the flaxseed mucilage as a by-product of the flaxseed oil extraction process.

Because mucilages also have hypoglycemic effects (Thakur *et al.*, 2009; Soukoulis, Gaiani, Hoffmann, 2018), it is possible that a synergism may exist when an antidiabetic drug, such as metformin HCl, is formulated using the flaxseed mucilage as the matrix. Moreover, these natural polymers have the potential to be a cheap and effective alternative to the current synthetic and semi-synthetic polymers used by the pharmaceutical industry, such as hydroxypropyl methylcellulose (HPMC). The aim of this work is to contribute to brown flaxseed mucilage applications by optimizing the development of an extended-release granule of metformin HCl through the design of experiments (DoE) methodology.

MATERIAL AND METHODS

All the reagents used in this study were of analytical grade.

MUCILAGE EXTRACTION AND DRYING

Brown flaxseeds were purchased from a local market in Niterói City, Rio de Janeiro, Brazil. The simplified mucilage extraction procedure was based on the works of Ziolkovska (2012), Cui *et al*. (1994), and Rocha *et al.* (2021b); it consisted of washing the whole seeds with distilled water, in a ratio of 1:13 m/v (seeds:water) at room temperature, with mechanical agitation of around 500 rotations per minute (RPM) (IKA Labortechnik RW 20DZM.n). The duration of the washing process was 24 h. Afterwards, the aqueous extract was filtered through regular, double-layered medical gauze to separate it from the seeds and subsequently lyophilized (LIOTOP L108) at -50 °C for 5 uninterrupted days. Then, the lyophilized solid mass was cut by a mixer (Mallory Trikxer 500) to disaggregate the fibers and reduce their size, allowing for their easy manipulation and simplify the manufacture of the granules.

FIBER CONTENT

The fiber content of the lyophilized flaxseed mucilage was determined through method AOAC 993.21 (2005), which evaluates total dietary fibers in foods and food products.

DESIGN OF EXPERIMENTS AND STATISTICAL ANALYSES

To determine the concentrations of metformin HCl and the mucilage in each tested formulation, a 3^2 factorial design with two replicates of the central point was chosen. Therefore, the concentrations of metformin HCl (Shouguang Fukang Pharmaceutical Co.) and the flaxseed mucilage were tested at three levels: 40, 60, and 80% and 8, 13, and 18%, respectively (Table I). The concentration of metformin HCl was defined based on the therapeutic dosage of the commercial medicine (500, 750, and 1000 mg), and the concentration of the mucilage was defined based on the concentration of metformin HCl. In addition, an extra formulation was manufactured with HPMC K4M (Colorcon, Inc.) instead of mucilage, using the central point configuration for comparison purposes. Microcrystalline cellulose 102 (Dupont Nutrition USA, Inc.) was used as the diluent and was therefore not considered in the experimental design.

TABLE I - Summary of the 3^2 DoE with two replicates of the central point, as well as the extra formulation containing HPMC used as a reference. Microcrystalline cellulose 102 was used as the diluent

Formulation number	Level and concentration of polymer	Level and concentration of metformin HCl
1	-1 (8%)	-1 (40%)
2	-1 (8%)	0 (60%)
3	-1 (8%)	+1 (80%)
4	0 (13%)	-1 (40%)
5	0 (13%)	0 (60%)
6	0 (13%)	+1 (80%)
7	+1 (18%)	-1 (40%)
8	+1 (18%)	0 (60%)
9	+1 (18%)	+1 (80%)
10	0 (13%)	0 (60%)
11	0 (13%)	0 (60%)
12 (HPMC)	0 (13%)	0 (60%)

The results were analyzed using Microsoft Excel® (RRID: SCR_016137) and Statistica® (RRID: SCR_014213) and compared through analysis of variance (ANOVA), considering a confidence level of 95% (i.e., $\alpha = 0.05$). Pareto charts and response surface graphs were chosen to illustrate the results.

PREPARATION OF THE GRANULES

The granules were prepared by a wet granulation method using 8 mL of ethanol 96 ºGL (Jalles Machado Co.); they were blended manually using a mortar and pestle, subsequently dried at 40 ºC in a Quimis Q317 drying oven, and finally calibrated in a 1.0 mm mesh. A 106 µm mesh was then used to separate any residual fine powder from the granules. Each formulation was tested to determine its drug concentration. Metformin HCl concentrations between 95 and 105% were accepted in accordance with the standard adopted by the Brazilian Pharmacopoeia (Brazil, 2019).

FRIABILITY TESTS

The friability tests were carried out according to an adapted method of the Brazilian Pharmacopoeia (Brazil, 2019). Friability was determined using a conventional rotative cylinder apparatus (PharmaTest D-63512 Hainburg) adapted with a cylindrical recipient to contain the granules. After calibration, 1.000 g of each formulation was tested. The results were collected after 100 rotations and were represented as the percentage of mass loss.

ANALYTICAL CURVES

The analytical curves were obtained in accordance with the Brazilian Pharmacopoeia (Brazil, 2019). Metformin HCl standards (4.00, 6.00, 8.00, 10.00, 12.00, 16.00, 20.00, and 30.00 µg/mL) were measured in water (for drug concentration determination) and in a pH 6.8 phosphate buffer (prior to the dissolution assays) using an ultraviolet (UV) spectrometer (UV-2600 Shimadzu) at a wavelength of 233 nm.

DRUG CONCENTRATION ASSAYS

The equivalent of 100 mg of metformin HCl was weighed and dissolved in water at a concentration of 1 mg/mL. The mixture was filtered using a vacuum system. An aliquot was obtained from the filtered solution in order to achieve the final concentration of 10 µL/mL. Then, the drug concentration was determined by UV spectrophotometry ($\lambda = 233$ nm) (Brazil, 2019).

DISSOLUTION ASSAYS

The dissolution assays were performed using a paddle apparatus (Quimis Q850), with some adaptations. The granules were confined inside inert capsules with sinkers. Phosphate buffer (pH of 6.8 at 37 ºC) was used as the medium, and the rotations of the paddles were set at 100 rpm (Brazil, 2019). Samples were collected at 5, 10, 20, 30, 45, 60, 90, 120, 150, 180, 210, 240, 300, and 360 min, diluted, and then analyzed using UV spectrophotometry ($\lambda = 233$ nm). The dissolution profiles were obtained,

and from them, the necessary time to dissolve 50 and 90% of the dosage form (T_{50} and T_{90}) and the dissolution efficiency (*DE*) were calculated (Khan, 1975) and used as a comparative parameter. The representative dissolution kinetic models of each dosage form were also discussed.

RESULTS AND DISCUSSION

Fiber content

The lyophilized mucilage was tested for total dietary fibers, and the results are summarized in Table II.

TABLE II - Results of the total fiber content of the lyophilized mucilage extracted from brown flaxseeds

Sample (g)	Fibers (g)	Ash (g)	Total fibers (%)
0.5008	0.2387	0.0221	43.05
0.5005	0.2350	0.0234	42.28
0.5006	0.2357	0.0226	42.57

The average total fibers percentage (42.63%) found in the lyophilized mucilage was higher than what was specified in the Brazilian Food Composition Table (TBCA) (33.5%) (Brazil, 2011) and what was reported by Barroso *et al.* (2014) (28.0%). A high fiber content suggests either high efficiencies of extraction and drying processes or a poor selectivity of the extraction method, which may result in the co-extraction of undesired substances of organic nature and/or other impurities. For example, cyanogenic glycosides are likely to be extracted along with the mucilage, which can then be removed by alcohol precipitation (Kaewmanee *et al.*, 2014).

However, the simplified extraction process used in this study deliberately lacks a purification process by considering economic and green chemistry principles. Since only water is necessary to mimic nature's extraction of the mucilage during the germination process of the flax plant, our simplified extraction procedure is a greener and more economical alternative, as large amounts of potentially harmful solvents are not required. In addition, solvent precipitation may co-precipitate other materials such as organic acids, certain salts, proteins and other similar substances (Vittori, 2002).

Friability tests

The results of the friability tests and other analyses regarding the granules are summarized in Table III and in the Pareto chart displayed in Figure 1.

TABLE III - Summary of the friability of the formulations (percentage of mass loss)

Formulation number	Level and percentage of polymer	Level and percentage of metformin HCl	Friability (percentage of mass loss)
1	-1 (8%)	-1 (40%)	7.05 ± 0.25
2	-1 (8%)	0 (60%)	7.10 ± 0.40
3	-1 (8%)	+1 (80%)	5.10 ± 0.80
4	0 (13%)	-1 (40%)	6.80 ± 0.40
5	0 (13%)	0 (60%)	5.65 ± 0.55
6	0 (13%)	+1 (80%)	5.35 ± 0.55
7	+1 (18%)	-1 (40%)	4.00 ± 0.40
8	+1 (18%)	0 (60%)	5.20 ± 0.30
9	+1 (18%)	+1 (80%)	2.55 ± 0.45
10	0 (13%)	0 (60%)	6.00 ± 0.20

TABLE III - Summary of the friability of the formulations (percentage of mass loss)

Formulation number	Level and percentage of polymer	Level and percentage of metformin HCl	Friability (percentage of mass loss)
11	0 (13%)	0 (60%)	6.75 ± 0.25
12 (HPMC)	0 (13%)	0 (60%)	5.55 ± 0.55

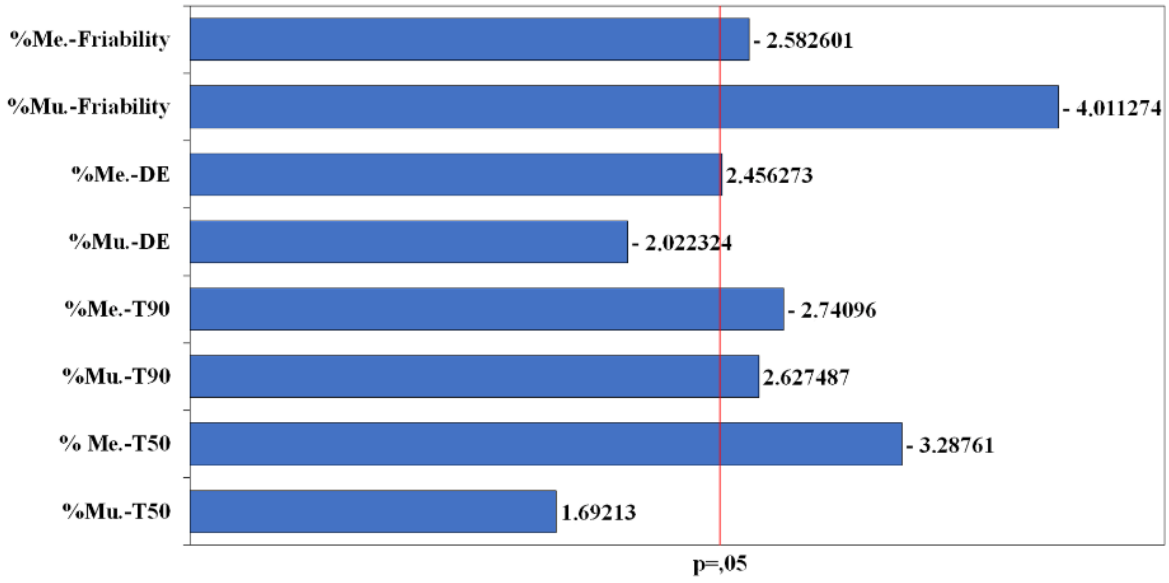

FIGURE 1 - Summary of the effects between dependent and independent variables. Mu. = Mucilage; Me. = Metformin HCl.

Granules are constantly subjected to physical stress during manufacture, storage and handling. These activities can negatively impact drug efficacy, because the production processes may result in the deformation or breakage of the granules. In addition, an excessively friable granule will easily break the homogeneity of the granule size within the dosage form. According to the literature, granule friability increases as the size of the granule decreases (Marks, Sciarra, 1968), and granule size can impact the characteristics of the tablets (Eichie, Kudehinbu, 2009; Monteyne *et al.*, 2016). Therefore, the friability test can help determine if the dosage form is stable enough to endure production and if the granules are suitable for compression.

The results of the friability tests are summarized in Table III and Figures 1 and 2. Higher concentrations of the mucilage and metformin HCl yielded a less friable granule. Furthermore, the influence of the mucilage concentration was significantly higher (p = 0.005234) than the metformin HCl concentration (p = 0.023989), which suggests that the polymers may help shield the components while providing proper mechanical resistance due to the high fiber content. The granules with HPMC showed similar results (5.55%) compared to the average friability of the manufactured granules (5.60%). These results may be considered high according to some authors, with some citing a limit of 1.7% (Gryczová, Dvořáčková, Rabišková, 2009). However, through different methods, values higher than 10% can be found in the literature as well (Keleb *et al.*, 2002; Van Melkebeke, Vervaet, Remon, 2008).

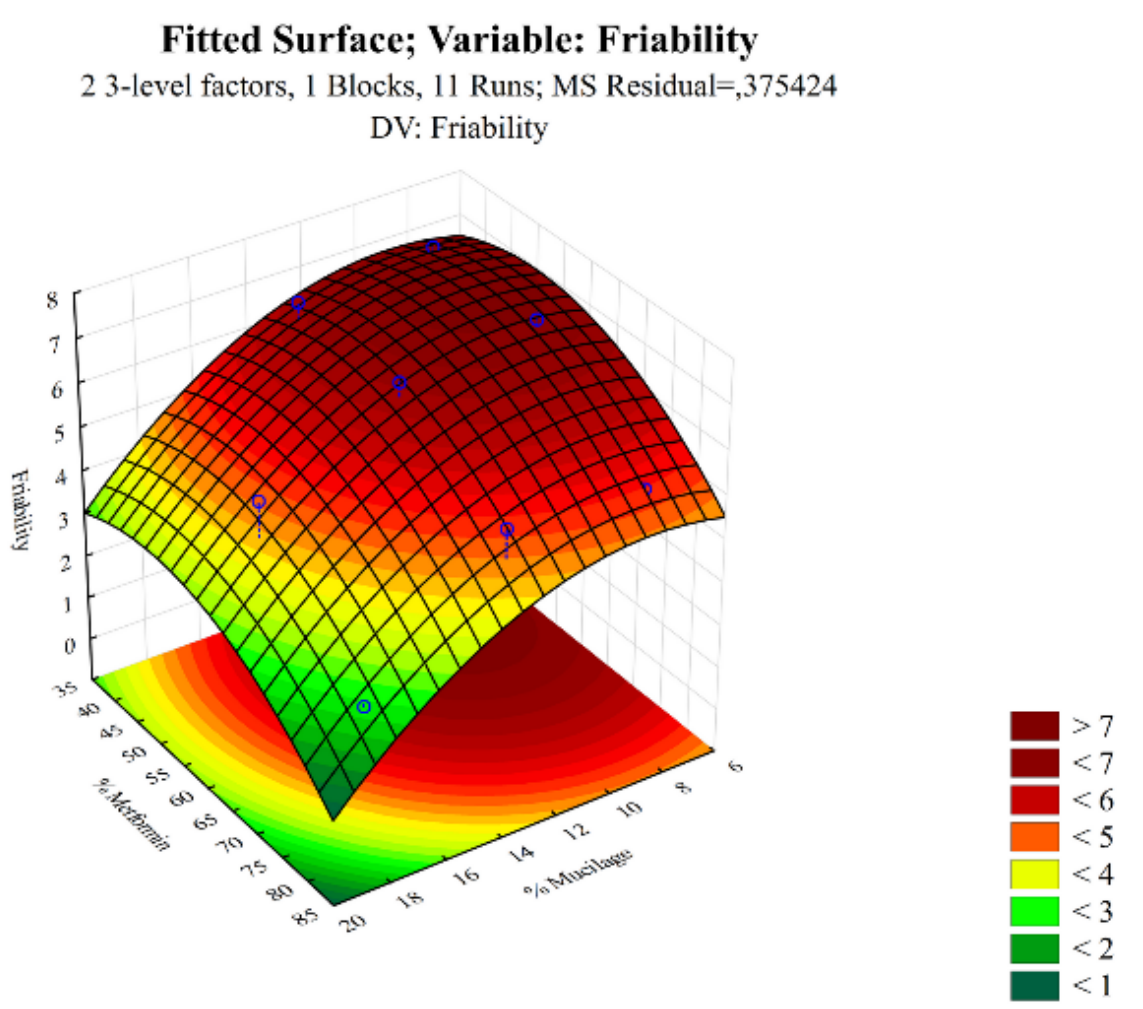

FIGURE 2 - Surface-response graph of the friability analyses. Higher concentrations of mucilage and metformin HCl yielded less friable granules.

DRUG CONCENTRATION ASSAYS

Each formulation presented drug concentrations between 95 and 105%, which indicates homogeneous handling and blending processes. The formulations were in accordance with the acceptable values specified by the Brazilian Pharmacopoeia (Brazil, 2019) (Table IV).

TABLE IV - Summary of the drug concentrations in the formulations (n = 3)

Formulation number	Average concentration (%)	Standard deviation (%)
1	103.20	0.81
2	101.28	1.47

TABLE IV - Summary of the drug concentrations in the formulations (n = 3)

Formulation number	Average concentration (%)	Standard deviation (%)
3	98.98	1.81
4	95.42	0.39
5	97.96	0.13
6	100.32	3.75
7	104.40	0.70
8	100.35	2.19
9	99.07	3.36
10	104.02	0.30
11	101.49	2.54

TABLE IV - Summary of the drug concentrations in the formulations (n = 3)

Formulation number	Average concentration (%)	Standard deviation (%)
12 (HPMC)	101.68	0.87

Dissolution assays

Most formulations (8 of 11) had dissolution kinetics better represented by the Hixson-Crowell model, including formulation 12 (containing HPMC K4M) (Table V). This model takes into consideration the geometrical shapes and surfaces of the formulation during dissolution. In this model, it is assumed that the release rate is limited by dosage form disintegration and the drug dissolution process and not by drug diffusion through the polymer matrix (Costa, Lobo, 2001). This behavior may imply that the polymer does not significantly impact the drug release mechanism, since this model is commonly used to interpret the dissolution of conventional and immediate release dosage forms (Gouda, Baishya, Qing, 2017). Nevertheless, the inclusion of HPMC granules in this group may indicate that the possible inability of the polymer matrix to define the kinetics is due to the tested dosage form. However, the higher concentrations of the mucilage (18%) present in formulations 7, 8, and 9 yielded dissolution kinetics that were better represented by the Korsmeyer-Peppas model, which is generally used to analyze the release of pharmaceutical polymeric dosage forms when more than one type of release phenomenon could be involved (Costa, Lobo, 2001). Therefore, it is possible that a higher concentration of the mucilage is required to achieve the appropriate release mechanism.

In addition, formulation 1 was better defined by the First Order model, which suggests that the release is influenced by the water-soluble drug concentration inside the porous matrix (Costa, Lobo, 2001).

TABLE V - Coefficient of determination (R^2) and release exponent (n) for each formulation, considering all the tested mathematical models. Considered time interval = 5–30 min

Formulation number	% Polymer*	% Metformin	Zero order	First order	Higuchi	Hixson-Crowell	Korsmeyer-Peppas		
			Coefficient of determination (R^2)					Release exponent (n)	Release mechanism
1	8	40	0.9671	**0.9847**	0.9211	0.9221	0.9618	0.9258	Non-Fickian
2	8	60	0.7367	0.6798	0.8268	**0.9875**	0.8502	0.3637	Fickian
3	8	80	0.7482	0.7378	0.8344	**0.9491**	0.9030	0.0594	Fickian
4	13	40	0.9798	0.9157	0.9991	**0.9994**	0.9959	0.6504	Non-Fickian
5	13	60	0.9442	0.8865	0.9846	**0.9952**	0.9850	0.4922	Fickian
6	13	80	0.8667	0.7867	0.9310	**0.9692**	0.9385	0.4337	Fickian
7	18	40	0.9985	0.9359	0.9940	0.9996	**0.9997**	0.8916	Non-Fickian
8	18	60	0.9971	0.9520	0.9728	0.9859	**0.9992**	1.1346	Super case II transport
9	18	80	0.8030	0.7728	0.8853	0.9256	**0.9265**	0.2083	Fickian

TABLE V - Coefficient of determination (R^2) and release exponent (n) for each formulation, considering all the tested mathematical models. Considered time interval = 5–30 min

Formulation number	% Polymer*	% Metformin	Zero order	First order	Higuchi	Hixson-Crowell	Korsmeyer-Peppas		
			Coefficient of determination (R^2)					Release exponent (n)	Release mechanism
10	13	60	0.8143	0.7056	0.8929	**0.9946**	0.8684	0.6626	Non-Fickian
11	13	60	0.9920	0.8980	0.9994	**0.9998**	0.9925	0.9872	Non-Fickian
12	13	60	0.9201	0.8632	0.9699	**0.9795**	0.9690	0.5114	Non-Fickian

* Formulation 1 to 11: Polymer = flaxseed mucilage. Formulation 12: Polymer = HPMC K4M.

Despite testing each formulation for 6 h (360 min), no single sample could surpass the 90-min mark, including the one containing HPMC. Regarding the dissolution profiles, five formulations (1 (8% Mu., 40% Me.), 4 (13% Mu., 40% Me.), 7 (18% Mu., 40% Me.), 8 (18% Mu., 60% Me.), and 11 (13% Mu., 60% Me.)) presented a longer release, while formulations 5 (13% Mu., 60% Me.) and 6 (13% Mu., 80% Me.) showed a similar profile compared to the reference containing HPMC K4M (Figure 3, Table VI). These results indicate that the flaxseed mucilage has the potential to act as a retardant agent, especially when the central points are compared to the HPMC formulation. In summary, the flaxseed mucilage may be extracted and used without any complex extraction and purification processes or the need of polymeric blends.

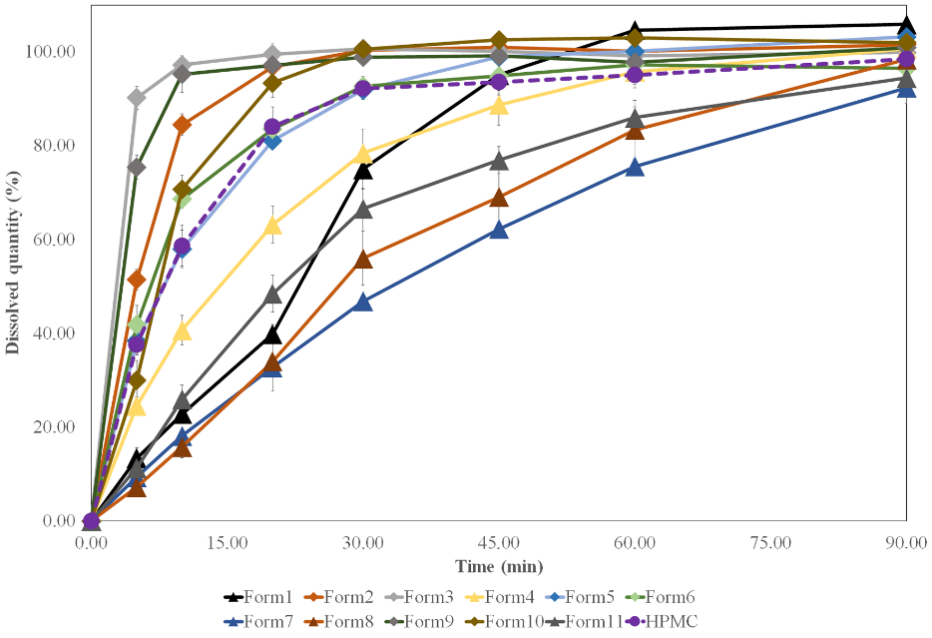

FIGURE 3 - Dissolution profiles of each formulation. Standard error $n = 3$.

Yadav and Jain (2015) and Rocha *et al.* (2021a) also evaluated the potential of the flaxseed mucilage compared to HPMC in a similar manner using tablets of diclofenac sodium and concluded that it has similar properties to well established polymers, and therefore it could replace them. Ghumman *et al.* (2020) evaluated microspheres of metformin HCl with a polymeric blend of the flaxseed mucilage and alginate, also with satisfying results. Additionally, Nayak *et al.* (2013a-d; 2014a-d) evaluated mucilages from different species blended with other polymers while using metformin HCl as the model drug with very promising results.

Regarding the dissolution profiles, the T_{50} and T_{90} values were lower when the metformin HCl concentration was high and the mucilage concentration was low (Figures 4 and 5). In this same configuration, the *DE* values were higher (Figure 6). However, only metformin HCl was considered a statistically significant variable regarding T_{50} and *DE* (Me.-T_{50} $p = 0.016663$; Me.-*DE* $p = 0.049369$), while both dependent variables were significant for T_{90} (Me.-T_{90} $p = 0.033692$; Mu.-T_{90} $p = 0.039191$). In other words, drug release can mainly depend on drug concentration and is facilitated in high concentrations. In addition, more time is necessary to dissolve 90% of the drug if the formulation contains a higher concentration of mucilage.

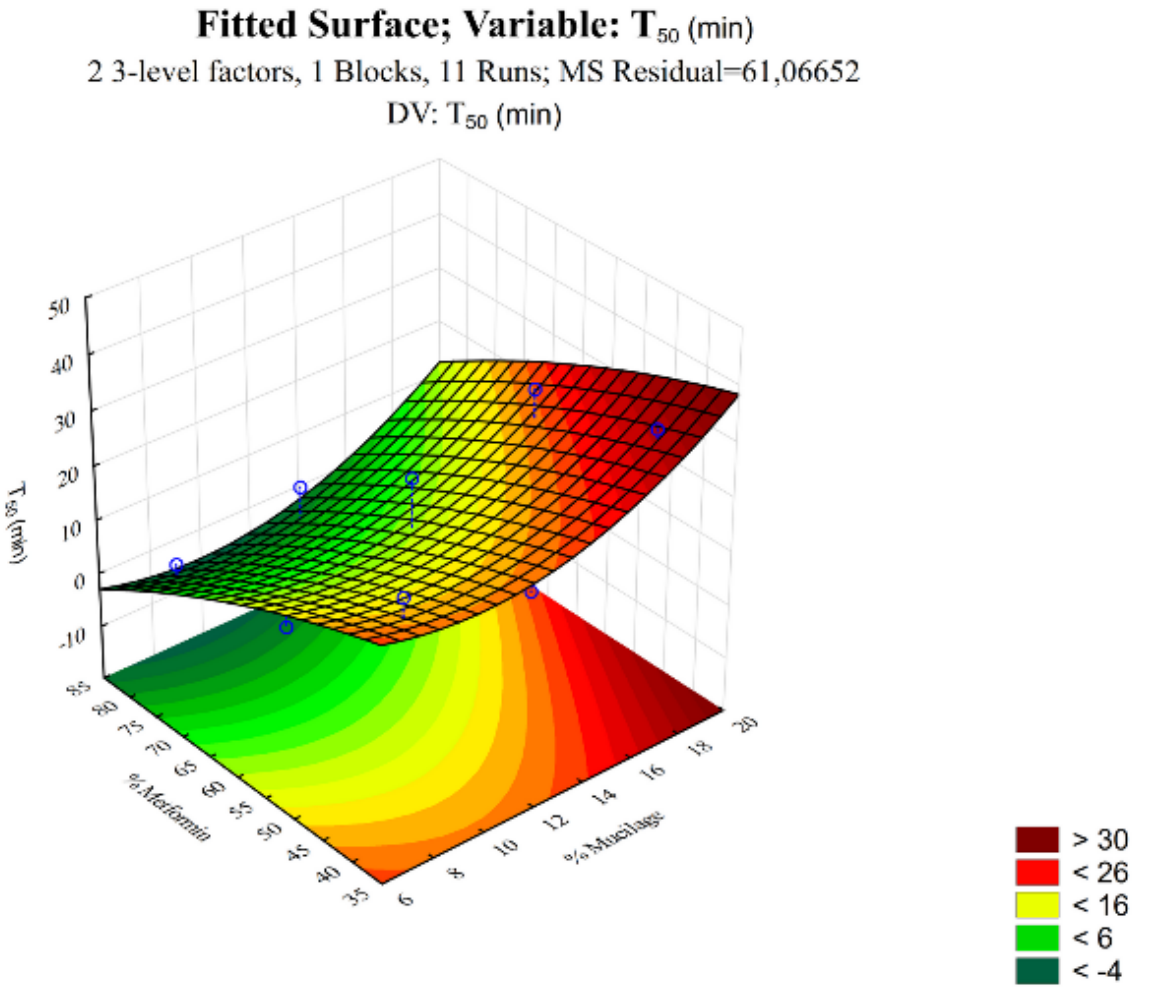

FIGURE 4 - Surface-response graph of the time necessary to dissolve 50% of a given formulation (T_{50}). Higher concentrations of metformin and lower concentrations of mucilage resulted in lower T_{50} values.

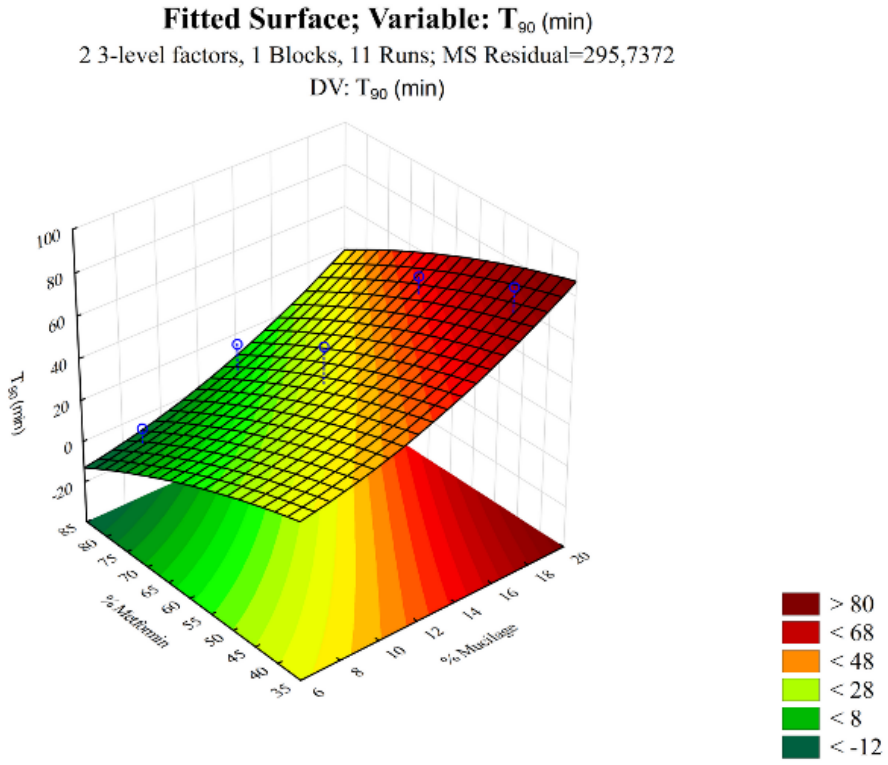

FIGURE 5 - Surface-response graph of the time necessary to dissolve 90% of a given formulation (T_{90}). Higher concentrations of metformin and lower concentrations of mucilage resulted in lower T_{90} values.

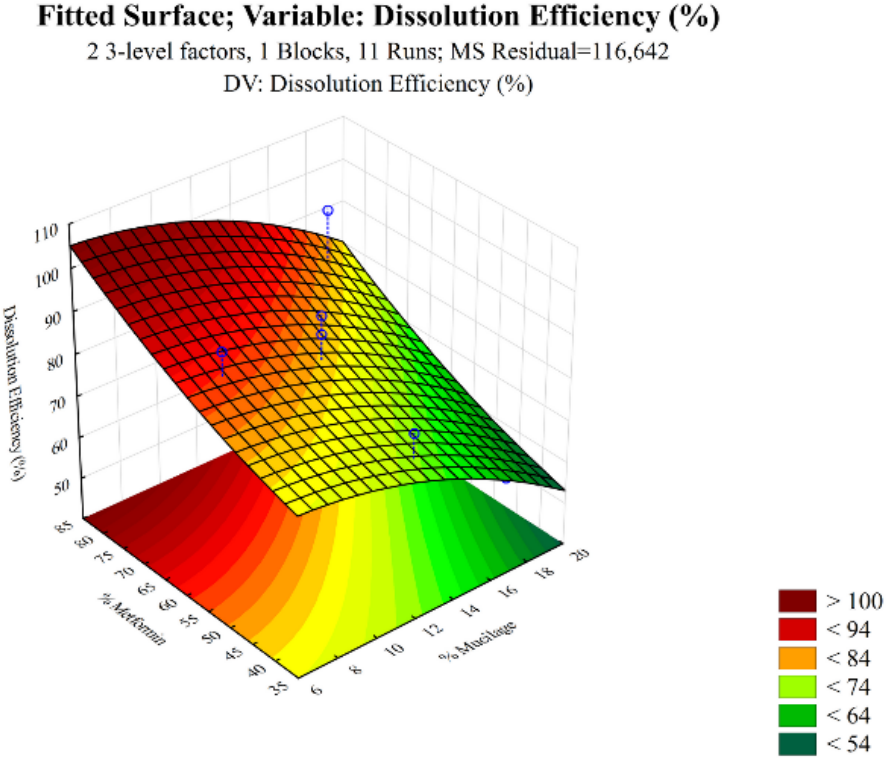

FIGURE 6 - Surface-response graph of dissolution efficiency. Higher concentrations of metformin and lower concentrations of mucilage resulted in higher dissolution efficiency.

TABLE VI - Summary of formulation characteristics and results

Formulation number	Level and concentration of polymer	Level and concentration of metformin HCl	Time to dissolve 50% (*T*50) (min)	Time to dissolve 90% (*T*90) (min)	Dissolution efficiency (%DE)
1	-1 (8%)	-1 (40%)	23.55	32.33	77.16
2	-1 (8%)	0 (60%)	3.76	13.86	93.38
3	-1 (8%)	+1 (80%)	*	*	96.31
4	0 (13%)	-1 (40%)	13.92	40.03	78.20
5	0 (13%)	0 (60%)	7.69	27.39	87.47
6	0 (13%)	+1 (80%)	5.31	25.75	86.43
7	+1 (18%)	-1 (40%)	32.77	85.40	56.85
8	+1 (18%)	0 (60%)	26.93	64.92	62.05
9	+1 (18%)	+1 (80%)	*	11.55	94.45
10	0 (13%)	0 (60%)	7.15	17.12	91.76
11	0 (13%)	0 (60%)	20.51	51.28	67.49
12 (HPMC)	0 (13%)	0 (60%)	7.38	26.01	84.88

*Incalculable values, quick dissolution.

CONCLUSION

The simplified extraction and lyophilization of the mucilage obtained from brown flaxseed resulted in a fibrous mass with a high total fiber content (42.63%) compared to the value described in the Brazilian Food Composition Table (33.5%), which may be indicative of the efficiency of our extraction process. The fibrous nature of the mucilage may help shield the granules developed in this study, providing them with increased mechanical resistance, because a higher concentration of the mucilage ($p = 0.005234$) yielded less friable granules. In addition, a higher concentration of metformin HCl ($p = 0.023989$) also contributed to this result.

Furthermore, higher concentrations of metformin HCl resulted in lower values for T_{50} ($p = 0.016663$) and T_{90} ($p = 0.033692$) and a higher DE ($p = 0.049369$). Higher concentrations of the mucilage resulted in higher T_{90} values ($p = 0.039191$). Thus, the drug release was mainly dependent on the drug concentration and was found to be facilitated by higher concentrations, while increased mucilage concentration helped delay drug release. Moreover, the kinetics of most formulations was better represented by the Hixson-Crowell model, whereas formulations with a higher mucilage concentration (18%) was represented by the Korsmeyer-Peppas model. Nonetheless, five formulations showed a longer release than the reference containing HPMC K4M. In short, the flaxseed mucilage has the potential to act as a retardant agent and can be obtained as nature intended: without a complex extraction and purification method, resulting in an economically viable and greener process. The mucilage also showed potential as a standalone polymer matrix, rendering the use of polymeric blends unnecessary. Overall, more desirable results were obtained at a higher concentration of the mucilage (13–18%) and a lower concentration of metformin (40%).

CONFLICTS OF INTEREST

All authors certify that they have no affiliations with or involvement in any organization or entity with any

financial or non-financial interest in the subject matter or the materials discussed in this manuscript. Therefore, the authors declare that there is no conflict of interest.

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